"-" is an amide, a substituted amide or an isostere of amide;

" = " is a covalent linkage; and

" ≡ " is a covalent linkage.

REMARKS

Claims 2-16, 18-30 and 34-48 are pending in this application. Claims 4 and 36 have been canceled in this amendment, without admission and without prejudice to Applicants' right to pursue the subject matter of those canceled claims in either this or other (*e.g.*, related) patent applications. Claims 2, 5, 9, 13, 15, 18-19, 23, 27, 34, 37, 41, and 45 have been amended without prejudice or admission by Applicants'. Thus, claims 1-3, 5-16, 18-30, 34-35 and 37-48 will be pending upon entry of these amendments.

The pending claims have been amended to clarify the subject matter of Applicants' invention. In particular, independent claims 2, 18 and 34 have been amended to more clearly specify that inhibitor compounds of the present invention comprises amino acid sequences for the particular TNF-R superfamily member TNF-R(I). For support, the Examiner's attention is respectfully direct to the Examples at the end of this application, and particularly to Example 2 at pages 36 to 39. These Examples describe in detail, experiments in which compounds were generated using binding sequences from crystal structures of TNF-R(I), and demonstrate that the compounds inhibit osteoclastogenesis by inhibiting another, different TNF-R

superfamily member, the TRANCE/RANK receptor. See, in particular, lines 9-27 on page 36 and lines 14-17 on page 37 of this application as filed.

The claims have also been amended to clarify the meaning of the phrase "capable of forming a covalent linkage", to which the Examiner has objected. The amended claims now particularly specify that the recited functional groups 'form' covalent linkages with the moieties specified, as illustrated in the original chemical diagrams accompanying the claims. Finally, claims 15 and 37 have been amended to correct certain typographical errors discovered by Applicants upon review of the pending claims. Specifically, claim 15 has been amended to capitalize the word Leu, and claim 37 to correctly specify an amino acid that "*is*" (rather than "*os*") a hydrophobic amino acid.

Thus, the amendments do not introduce new matter to the pending claims. Entry and consideration of these amendments are respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 2-16, 18-30 and 34-48 have been rejected under 35 U.S.C. § 112, first paragraph as being indefinite. In particular, the Examiner has objected to the phrase "capable of forming" and indicates that the term is confusing.

In response, Applicants respectfully submit that the meaning to a person skilled in the art when the pending claims are read in the context of this application as filed. In particular, the original claims and specification as filed

provide chemical formulas for the compounds of this application, with lines indicating covalent bonds (*i.e.*, covalent "linkages") between the different chemical moieties. Clearly, therefore, each of the moieties must be "capable of forming" such covalent bonds with each other to form the recited compounds.

Nevertheless, Applicants have amended the pending claims to remove the term "capable of forming." The claims now simply specify that the specified functional groups form certain, particular covalent bonds with other moieties in the recited compounds. Applicants believe that the pending claims are fully definite within the meaning of 35 U.S.C. § 112, second paragraph, and respectfully request that this rejection be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 2-16, 18-30 and 34-48 have also been rejected under 35 U.S.C. § 103(a) as being obvious over the reference of Yamaguchi *et al.*, *J. Biol. Chem.* 1998, 273(9):5117-5123 ("Yamaguchi") in view of International Patent Publication No. WO 98/53842 by Greene *et al.* ("Greene"). In particular, Yamaguchi is said to teach another member of the TNF-R family, referred to as the

osteoclastogenesis inhibitory factor (OCIF),[1] and the use of OCIF peptides to inhibit osteoclastogenesis. Greene is said to teach the peptide inhibitors of this invention. Specifically, Greene allegedly teaches "peptides and peptide analogues designed from a binding loop of a member of the [TNF-R] superfamily." Greene also allegedly teaches the use of such peptides and/or peptide analogues to inhibit a TNF receptor. Accordingly, the Examiner concludes that the skilled artisan would reasonably expect that the peptides and/or peptide analogues taught be Greene would successfully inhibit the OCIF receptor described by Yamaguchi and thereby inhibit osteoclastogenesis and bone resorption. Applicants respectfully submit that this rejection should be withdrawn, for the reasons discussed in detail below.

Three basic criteria must be met to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a reasonable expectation that the modifications or combination would succeed. Finally, the combined or modified prior art must actually teach all of the claimed limitations. Both the motivation and the reasonable expectation of success must be found in the prior art and not in

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[1]Although it is not believed to be particularly relevant to the present obviousness rejection, Applicants note that the OCIF polypeptide described by Yamaguchi (also referred to as osteoprotegrin) is now commonly referred to in the art and in this application as TRANCE/RANK. See, *e.g.*, lines 20-27 on page 2 of this application as filed.

Applicants' disclosure. *See*, M.P.E.P. § 2143; citing *In re Vaeck* , 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the present invention, the claimed methods are ones that use peptides and/or peptide inhibitors designed from a *particular* TNF-R family member; TNF-R(I). Applicants have discovered that, surprisingly, these peptides also inhibit a *different* TNF-R family member; TRANCE/RANK. TRANCE/RANK is a TNF receptor that regulates osteoclastogenesis and the resorbing activity of mature osteoclast cells. Thus, by their unexpected discovery Applicants have found that the TNF-R(I) peptides and/or peptide inhibitors of this invention can be used in novel methods, to inhibit osteoclastogenesis and bone resorption.

The relevant inquiry for obvious is therefore whether a skilled artisan would have been motivated to use the TNF-R(I) peptides and/or peptide inhibitors of this invention to inhibit a different TNF-R family member, such as the OCIF polypeptide taught by Yamaguchi.[2] It is not enough to merely show that a skilled artisan may have been motivated to *try* such a method. The invention must also be apparent with a reasonable expectation of success. Thus, it must also be shown that the TNF-R(I) peptides and/or peptide inhibitors of this invention would have been reasonably expected to inhibit the OCIF polypeptide, and that this would successfully inhibit osteoclastogenesis and/or bone resorption. As explained in

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[2] *i.e.*, TRANCE/RANK; as noted *supra* (see footnote 1) TRANCE/RANK is identical to the OCIF TNF-R family member described by Yamaguchi.

detail below, neither the motivation nor any reasonable expectation of success is provide by the cited references, when considered either alone or in combination with each other.

Greene merely describes, at best, TNF-R(I) derived peptides and peptide inhibitors. Yet, Greene only describes the use of those compounds to inhibit the very TNF-R family member from which they are derived, TNF-R(I). Contrary to what is indicated in the Office Action, Greene does not teach or suggest that these TNF-R(I) derived compounds may successfully inhibit any other TNF-R family member, much less their use to inhibit TRANCE/RANK (*i.e.*, OCIF). Instead, Greene only states that:

> "corresponding regions of other TNF-R superfamily members from which inhibitory peptides and peptide analogues can be designed are readily identified by amino acid sequence alignment with the three specific binding cites of TNF-R p55. . . . [T]he same region in each TNF-R superfamily member may be used to design peptides and peptide analogues."[3]

Such teaching only suggest that, given a peptide inhibitor derived from one TNF-R superfamily member (*e.g.*, TNF-R(I)), a skilled artisan might be able to derived other inhibitors from a *different* TNF-R superfamily member (*e.g.*, OCIF) by aligning the different TNF-R protein sequences and selecting peptides from

---

[3]*See*, in particular, lines 9-17 on page 11 of Greene.

corresponding regions. This only means, however, that given the combination of Greene and Yamaguchi, the skilled artisan could have only been motivated (if at all) to derive different peptide inhibitors corresponding to those OCIF sequences which align with the corresponding TNF-R(I) sequences of Greene.

Yamaguchi does not overcome any of the deficiencies in Greene. Instead, Yamaguchi is only said to teach that the N-terminal portion of OCIF is sufficient to inhibit osteoclastogenesis. *See*, lines 4-7 on page 5 of the Office Action. Yet, again, this only provides (at best) motivation to use an OCIF derived peptide from this region to inhibit OCIF activity. Yamaguchi does not provide *any* suggestion that a peptide derived from a *different* TNF-R family member (*e.g.*, TNF-R(I)) might be used to inhibit OCIF. Nor does Yamaguchi provide any reasonable expectation that such a TNF-R(I) peptide or peptide inhibitor may successfully inhibit either osteoclastogenesis or bone resorption.

For all of the above reasons, therefore, Applicants respectfully submit that the obviousness rejection has been obviated and should be withdrawn.

CONCLUSION

For the reasons stated above, Applicants believe that all of the outstanding rejections to this application have been overcome and/or obviated, and that the claims are in condition for allowance. The withdrawal of all objections and rejections, and reconsideration of the application are therefore respectfully

requested. The Examiner is also invited to contact Applicant's undersigned representative at the telephone number indicated below if (s)he believes that it would advance the prosecution of this application. An allowance is earnestly sought.

Respectfully submitted,

Dated: June 14, 2002

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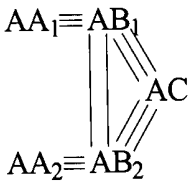
EXHIBIT A:
AMENDMENTS MADE TO PENDING CLAIMS
U.S. PATENT APPLICATION SERIAL NO. 09/627,775
(ATTORNEY DOCKET NO. 4040/1K200-US1)

SUBMITTED PURSUANT TO 37 C.F.R. § 1.121(C)(1)(ii)

2. (Twice Amended) A method of inhibiting osteoclastogenesis comprising the steps of administering to a patient an amount of an inhibitor effective to inhibit osteoclastogenesis, wherein the inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of [a TNF-R superfamily member] TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB_1 is a moiety having a first functional group [capable of] forming a covalent linkage with one terminus of AC, a second functional group [capable of] forming a covalent linkage with AB_2 and a third functional group [capable of] forming a covalent linkage with AA_1 ;

AB_2 is a moiety having a first functional group [capable of] forming a covalent linkage with the second terminus of AC, a second functional group [capable of] forming a covalent linkage with AB_1 and a third functional group [capable of] forming a covalent linkage with AA_2;

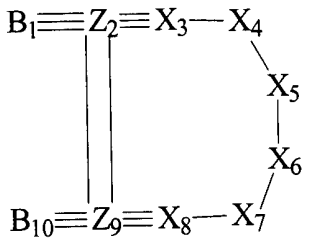
AA_1 is a moiety having hydrophobic properties and a functional group [capable of] forming a covalent linkage with the third functional group of AB_2;

AA_2 is a moiety having hydrophobic properties and a functional group [capable of] forming a covalent linkage with the third functional group of AB_2;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

5. (Amended) The method of Claim 4 wherein the inhibitor has the formula:



(II)

wherein:

B_1 and B_{10} are each independently a peptide of 1-6 amino acids at least one of which os a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_2 is a moiety [that is capable of] forming a covalent linkage with B_1 , X_3 and Z_9;

Z_9 is a moiety [that is capable of] forming a covalent linkage with B_{10}, X_8 and Z_2;

X_3 is absent or a hydrophilic amino acid;

X_4 is a hydrophobic amino acid;

X_5 is a hydrophobic amino acid;

X_6 is a hydrophobic amino acid;

X_7 is a hydrophobic or hydrophilic amino acid;

X_8 is a hydrophobic or hydrophilic amino acid;

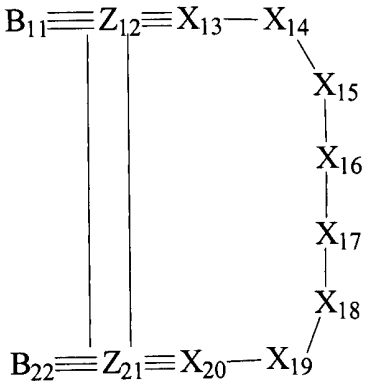
"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

9. (Amended) The method of Claim 4, wherein the inhibitor has the formula:

(III)



wherein:

B_{11} and B_{22} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{12} is a moiety [that is capable of] forming a covalent linkage with B_{11}, X_{13} and Z_{21};

Z_{21} is a moiety [that is capable of] forming a covalent linkage with B_{22}, X_{20} and Z_{12};

X_{13} is absent or hydrophobic amino acid;

X_{14} is absent or hydrophilic amino acid;

X_{15} is a hydrophilic or hydrophobic amino acid;

X_{16} is a hydrophilic amino acid;

X_{17} is absent or a hydrophobic amino acid;

X_{18} is a hydrophilic amino acid;

X_{19} is a hydrophilic amino acid;

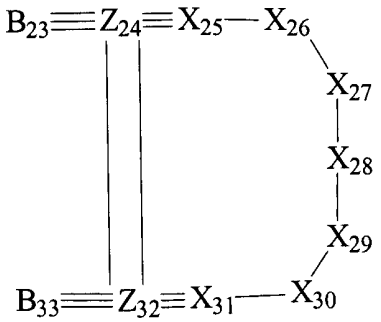
X_{20} is a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

13. (Amended) The method of Claim 4, wherein the inhibitor has the formula:

(IV) 

wherein:

B_{23} and B_{33} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{24} is a moiety [that is capable of] forming a covalent linkage with B_{23}, X_{25} and Z_{32};

Z_{32} is a moiety [that is capable of] forming a covalent linkage with B_{33}, X_{31} and Z_{24};

X_{25} is absent or a hydrophilic amino acid;

X_{26} is a hydrophilic amino acid;

X_{27} is a hydrophilic amino acid;

X_{28} is a hydrophilic amino acid;

X_{29} is a hydrophilic amino acid;

X_{30} is absent or a hydrophilic amino acid;

X_{31} is absent or a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

15. (Amended) The method of Claim 14, wherein:

B_{23} and B_{33} are each independently Tyr or Phe;

Z_{24} and Z_{32} are each Cys;

X_{25} is absent or Arg;

X_{26} is Lys;

X_{27} is Glu;

X_{28} is [leu] Leu, Pro or Met;

X_{29} is Gly;

X_{30} is absent or Gln;

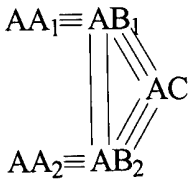
X_{31} is absent or Val;

"-" is an amide linkage;

"=" is a disulfide linkage; and

"≡" is an amide linkage.

18. (Twice amended) A method of treating patients who have diseases characterized by bone loss comprising the step of administering to said patient an amount of an inhibitor effective to inhibit such bone loss, wherein said inhibitor is a compound having the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of [a TNF-R superfamily member] TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB_1 is a moiety having a first functional group [capable of] forming a covalent linkage with one terminus of AC, a second functional group [capable of]

forming a covalent linkage with AB_2 and a third functional group [capable of] forming a covalent linkage with AA_1;

AB_2 is a moiety having a first functional group [capable of] forming a covalent linkage with the second terminus of AC, a second functional group [capable of] forming a covalent linkage with AB_1 and a third functional group [capable of] forming a covalent linkage with AA_2;

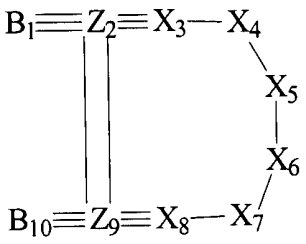
AA_1 is a moiety having hydrophobic properties and a functional group [capable of] forming a covalent linkage with the third functional group of AB_1;

AA_2 is a moiety having hydrophobic properties and a functional group [capable of] forming a covalent linkage with the third functional group of AB_2;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

19. (Amended) The method of claim 18 wherein the compound has the formula:



(II)

wherein:

B_1 and B_{10} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_2 is a moiety that is [capable of] forming a covalent linkage with B_1, X_3 and Z_9;

Z_9 is a moiety that is [capable of] forming a covalent linkage with B_{10}, X_8 and Z_2;

X_3 is absent or a hydrophilic amino acid;

X_4 is a hydrophobic amino acid;

X_5 is a hydrophilic amino acid;

X_6 is a hydrophilic amino acid;

X_7 is a hydrophobic or hydrophilic amino acid;

X_8 is a hydrophobic or hydrophilic amino acid;

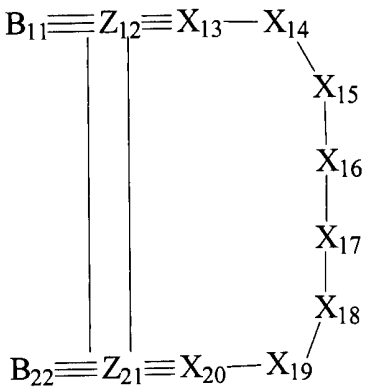
"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

23. (Amended) The method of claim 18 wherein the compound has the formula:

(III)



wherein:

B_{11} and B_{22} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{12} is a moiety [that is capable of] forming a covalent linkage with B_{11}, X_{13} and Z_{21};

Z_{21} is a moiety [that is capable of] forming a covalent linkage with B_{22}, X_{20} and Z_{12};

X_{13} is absent or hydrophobic amino acid;

X_{14} is absent or a hydrophilic amino acid;

X_{15} is a hydrophilic or hydrophobic amino acid;

X_{16} is a hydrophilic amino acid;

X_{17} is absent or a hydrophobic amino acid;

X_{18} is a hydrophilic amino acid;

X_{19} is a hydrophilic amino acid;

X_{20} is a hydrophilic amino acid;

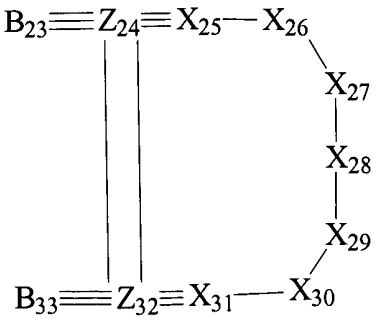
"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

27. (Amended) The method of claim 18 wherein the compound has the formula:

(IV)



wherein:

B_{23} and B_{33} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{24} is a moiety [that is capable] of forming a covalent linkage with B_{23}, X_{25} and Z_{32};

Z_{32} is a moiety [that is capable] of forming a covalent linkage with B_{33}, X_{31} and Z_{24};

X_{25} is absent or a hydrophilic amino acid;

X_{26} is a hydrophilic amino acid;

X_{27} is a hydrophilic amino acid;

X_{28} is a hydrophobic amino acid;

X_{29} is a hydrophobic amino acid;

X_{30} is absent or a hydrophobic amino acid;

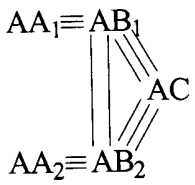
X_{31} is absent or a hydrophobic amino acid;

"-" is an amide, a substituted amide or an isostere of amide;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

34. (Twice amended) A method of inhibiting bone resorption comprising the step of administering to a patient an amount of an inhibitor effective to inhibit bone resorption, wherein said inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of [a TNF-R superfamily member] TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB_1 is a moiety having a first functional group [capable of] forming a covalent linkage with one terminus of AC, a second functional group [capable of] forming a covalent linkage with AB_2 and a third functional group [capable of] forming a covalent linkage with AA_1 ;

AB_2 is a moiety having a first functional group [capable of] forming a covalent linkage with the second terminus of AC, a second functional group [capable of] forming a covalent linkage with AB_1 and a third functional group [capable of] forming a covalent linkage with AA_2;

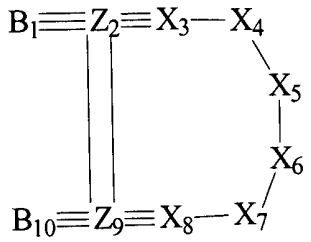
AA_1 is a moiety having hydrophobic properties and a functional group [capable of] forming a covalent linkage with the third functional group of AB_2;

AA_2 is a moiety having hydrophobic properties and a functional group [capable of] forming a covalent linkage with the third functional group of AB_2;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

37. (Amended) The method of Claim 36 wherein the inhibitor has the formula:



(II)

wherein:

B_1 and B_{10} are each independently a peptide of 1-6 amino acids at least one of which [os] is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_2 is a moiety [that is capable of] forming a covalent linkage with B_1 , X_3 and Z_9;

Z_9 is a moiety [that is capable of] forming a covalent linkage with B_{10}, X_8 and Z_2;

X_3 is absent or a hydrophilic amino acid;

X_4 is a hydrophobic amino acid;

X_5 is a hydrophobic amino acid;

X_6 is a hydrophobic amino acid;

X_7 is a hydrophobic or hydrophilic amino acid;

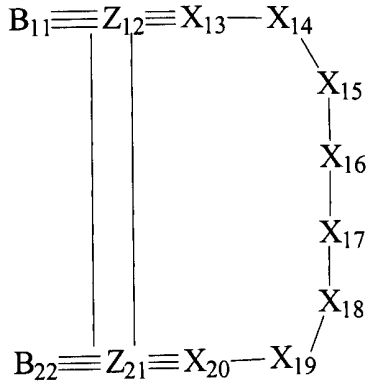
X_8 is a hydrophobic or hydrophilic amino acid;

"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

41. (Amended) The method of Claim 36, wherein the inhibitor has the formula:

(III) 

wherein:

B_{11} and B_{22} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{12} is a moiety [that is capable of] forming a covalent linkage with B_{11}, X_{13} and Z_{21};

Z_{21} is a moiety [that is capable of] forming a covalent linkage with B_{22}, X_{20} and Z_{12};

X_{13} is absent or hydrophobic amino acid;

X_{14} is absent or hydrophilic amino acid;

X_{15} is a hydrophilic or hydrophobic amino acid;

X_{16} is a hydrophilic amino acid;

X_{17} is absent or a hydrophobic amino acid;

X_{18} is a hydrophilic amino acid;

X_{19} is a hydrophilic amino acid;

X_{20} is a hydrophilic amino acid;

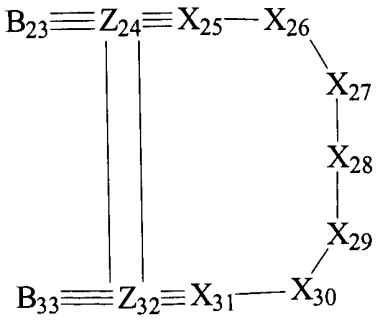
"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

45. (Amended) The method of Claim 36, wherein the inhibitor has the formula:

(IV)



wherein:

B_{23} and B_{33} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{24} is a moiety [that is capable of] forming a covalent linkage with B_{23}, X_{25} and Z_{32};

Z_{32} is a moiety [that is capable of] forming a covalent linkage with B_{33}, X_{31} and Z_{24};

X_{25} is absent or a hydrophilic amino acid;

X_{26} is a hydrophilic amino acid;

X_{27} is a hydrophilic amino acid;

X_{28} is a hydrophilic amino acid;

X_{29} is a hydrophilic amino acid;

X_{30} is absent or a hydrophilic amino acid;

X_{31} is absent or a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide;

"=" is a covalent linkage; and

"≡" is a covalent linkage.